

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/16/2010 has been entered.

Response to Amendment

2. The declaration of Hoon under 37 CFR 1.132 filed 12/16/2010 is insufficient to overcome the rejection of claims 103-132 based upon Soegnas and Fujiwara as set forth in the last Office action because: MPEP 716.01 (c) states: "In assessing the probative value of an expert opinion, the examiner must consider the nature of the matter sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion." MPEP 716.01 (c) further states, "Although factual evidence is preferable to opinion testimony, such testimony is entitled to consideration and some weight so long as the opinion is not on the ultimate legal conclusion at issue. While an opinion as to a legal conclusion is not entitled to any weight, the underlying basis for the opinion may be persuasive." Finally, MPEP 716.01 (C) states, "An affidavit of an applicant as to the advantages of his or her claimed invention, while less persuasive than that of a disinterested person, cannot be disregarded for this reason alone." In the

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instant case the declaration is presented by inventor Hoon and establishes his credentials as a molecular oncologist. The declaration is thus presented by a person with an interest in the instant application. The declaration reviews the Soengas teachings and notes that Soengas does not direct one of skill in the art to examine acellular DNA for survival, prognosis or cancer therapy response. The response continues by asserting, " One of ordinary skill in the art could not reasonably predict or assume that LOH of microsatellite DNA markers in a melanoma metastatic tumor would be the same in the acellular DNA derived from a metastatic melanoma patient's blood. For example, in Fujiwara et al., (Cancer Research, 1999, volume 59, pages 1567-1571) ("Fujiwara"), we demonstrated, that while LOH of microsatellite markers can be determined from acellular DNA, the LOH of microsatellite markers from informative metastatic melanoma tumors and informative acellular DNA from metastatic melanoma patients were not identical or predictable. One of ordinary skill in the art would not be enabled, let alone expect to predict the probability of survival, prognosis, or cancer therapy efficacy based upon the LOH data in Soengas because as shown in Fujiwara, merely detecting LOH of a microsatellite marker does not predict prognosis, outcome or efficacy of treatment." These arguments have been thoroughly reviewed but are not considered persuasive as the instant rejection and claims are not drawn merely to the detection of a single LOH event, as asserted but predicting subjects with loss of heterozygosity of one or more DNA has a negative outcome. While the declaration asserts unpredictability it does not present any data. Further, these arguments appear to assert the instant claims are not enabled as the specification as filed only provides

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data correlating LOH of the accellular markers with respect to biochemotherapy prior to treatment with the biochemotherapy and survival after treatment with a single type of biochemotherapy. The prior art of Fujiwara teaches, "The frequency and the number of microsatellite markers with LOH in plasma significantly increased in more advanced clinical stages of disease. These findings support previous work on melanoma and other cancers that show that as tumors progress, the number of genetic changes accumulates" (1570). Fujiwara concludes, "The analysis of LOH in plasma provides a logistically practical assay to monitor genetic changes during melanoma progression. The study demonstrates that at early clinical stages, release of DNA (LOH marker) is limited. Plasma LOH analysis may be more suitable to monitor stage II to stage IV progression before and during therapy as well as during post treatment follow-up. The markers may be also useful to detect subclinical disease recurrence in disease-free patients. Tumor progression is dynamic, and the genetic changes that concurrently occur are also ongoing. The most significant advantage of this approach in assessing plasma compared with direct analysis of tumor biopsies is the ability to monitor disease progression and genetic changes without assessing the tumor. This is particularly important during early phases of distant disease spread in which subclinical disease is undetectable by conventional imaging techniques. Additional retrospective and prospective analyses are being carried out to determine the prognostic significance of the DNA microsatellite markers during treatment and as overall predictors of disease outcome" (1571). Thus as the declaration provides no specific evidence and Fujiwara

indicates that increasing levels of LOW are indicative of advanced clinical disease the arguments are not persuasive.

Claim status and Formal matters

This action is in response to papers filed 12/16/2010.

All previous claims have been canceled. Thus all previous claim rejections have been withdrawn.

The interview record is complete. It is noted that as indicated in the response the examiner (at time of interview) did suggest that amending the claims to be directed to determining increased likelihood of type III or type IV melanoma by detection of the claimed markers in conjunction with a declaration from Dr. Hoon may overcome the obviousness type rejections. It is noted the instant claims are not drawn to the suggested invention and Dr. Hoon has provided a declaration, but has not provided data described in the discussion of the interview supporting the assertions that LOH of the claimed markers is found in Type III and IV melanoma, but not other types.

All previous rejections are withdrawn as all previous claims are canceled.

Claims 103-132 are pending.

Drawings

3. The drawings are objected to because the figures are not labeled consistent with 37 CFR 1.84 (u) (1) which requires The different views must be numbered in consecutive Arabic numerals, starting with 1, independent of the numbering of the sheets and, if possible, in the order in which they appear on the drawing sheet(s). Partial views intended to form one complete view, on one or several sheets, must be

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identified by the same number followed by a capital letter. View numbers must be preceded by the abbreviation "FIG. " Where only a single view is used in an application to illustrate the claimed invention, it must not be numbered and the abbreviation "FIG. " must not appear.. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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5. Claims 103-132 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method of predicting metastatic melanoma survival comprising: providing a blood, serum or plasma sample containing acellular DNA from a human subject suffering from metastatic melanoma; comparing DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346 in the acellular DNA with the same DNA markers in a control DNA from subject peripheral blood lymphocytes; determining from the comparison step if the acellular DNA has a loss of heterozygosity at one or more of the DNA markers; and predicting that the subject having a loss of heterozygosity at one or more of the DNA markers has a lower probability of survival than a subject with no loss of heterozygosity.

However, the specification and prior art do not reasonably provide enablement for comparison to any control sample. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in *re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the *Ex parte Forman*.

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They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and the breadth of the claims:

Claim 103 is drawn to a method of predicting metastatic melanoma survival comprising: providing a blood, serum or plasma sample containing acellular DNA from a human subject suffering from metastatic melanoma; comparing DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346 in the acellular DNA with the same DNA markers in a control DNA; determining from the comparison step if the acellular DNA has a loss of heterozygosity at one or more of the DNA markers; and predicting that the subject having a loss of heterozygosity at one or more of the DNA markers has a lower probability of survival.

Thus claim 103 encompasses the loss of heterozygosity of one or more alleles of the claimed markers relative to any control from any species are indicative of a lower probability of survival.

Claim 104 depends from claim 103 and draws the invention to wherein the acellular and control DNA are amplified.

Claim 105 depends from claim 103 and draws the invention to wherein the control DNA is obtained from non- neoplastic tissue from the subject.

Claim 106 depends from claim 103 and draws the invention to wherein the control DNA is obtained from a biological fluid or tissue from a normal subject.

Thus claim 106 encompasses the use of control DNA from any "biological fluid" or "tissue" of any subject from any species.

Claim 107 depends from claim 103 and draws the invention to wherein the control DNA is obtained from peripheral blood lymphocytes from the subject.

Claim 108 depends from claim 103 and draws the invention to wherein the loss of heterozygosity comprises a 40% or more reduction of peak intensity for the acellular DNA marker as compared to the corresponding control DNA marker.

Independent claim 109 is drawn to a method of metastatic melanoma prognosis comprising: providing a blood, serum or plasma sample containing acellular DNA from a human subject suffering from metastatic melanoma; comparing DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346 in the acellular DNA with the same DNA markers in a control DNA; determining from the comparison step if the acellular DNA has a loss of heterozygosity at one or more of the DNA markers; and predicting that the subject having a loss of heterozygosity at one or more of the DNA markers has a poor prognosis.

Thus claim 109 encompasses the loss of heterozygosity of one or more alleles of the claimed markers relative to any control from any species is indicative of a lower probability of survival.

Claim 110 depends from claim 109 and draws the invention to wherein the acellular and control DNA are amplified.

Claim 111 depends from claim 109 and draws the invention to wherein the control DNA is obtained from non- neoplastic tissue from the subject.

Claim 112 depends from claim 109 and draws the invention to wherein the control DNA is obtained from a biological fluid or tissue from a normal subject.

Claim 113 depends from claim 109 and draws the invention to wherein the control DNA is obtained from peripheral blood lymphocytes from the subject.

Claim 114 depends from claim 109 and draws the invention to wherein the loss of heterozygosity comprises a 40% or more reduction of peak intensity for the acellular DNA marker as compared to the corresponding control DNA marker.

Independent claim 115 is drawn to a method of predicting efficacy of melanoma cancer therapy comprising: providing a blood, serum or plasma sample containing acellular DNA from a human subject suffering from Stage IV melanoma prior to administration of a cancer therapy; comparing DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346 in the acellular DNA with the same DNA markers in a control DNA; determining from the comparison step if the acellular DNA has a loss of heterozygosity at one or more of the DNA markers; and predicting that the cancer therapy efficacy of the subject having a loss of heterozygosity one or more of the DNA markers will likely be poor.

Claim 116 depends from claim 115 and draws the invention to wherein the cancer therapy is selected from the group consisting of chemotherapy, radiation

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therapy, gene therapy, immunotherapy, surgical procedure, and a combination of the cancer therapies.

Claim 117 depends from claim 115 and draws the invention to wherein the cancer therapy is biochemotherapy.

Claim 1118 depends from claim 117 and draws the invention to wherein the cancer therapy is biochemotherapy and is a combination selected from the group consisting of dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2, and tamoxifen.

Claim 119 depends from claim 115 and draws the invention to wherein the acellular and control DNA are amplified.

Claim 120 depends from claim 115 and draws the invention to wherein the control DNA is obtained from non- neoplastic tissue from the subject.

Claim 121 depends from claim 115 and draws the invention to wherein the control DNA is obtained from a biological fluid or tissue from a normal subject.

Claim 122 depends from claim 115 and draws the invention to wherein the control DNA is obtained from peripheral blood lymphocytes from the subject.

Claim 123 depends from claim 115 and draws the invention to wherein the loss of heterozygosity comprises a 40% or more reduction of peak intensity for the acellular DNA marker as compared to the corresponding control DNA marker.

Independent claim 124 is drawn to a method of predicting responsiveness to cancer therapy comprising: providing a blood, serum or plasma sample containing acellular DNA from a human subject suffering from Stage IV melanoma prior to administration of a cancer therapy; comparing DNA markers selected from the group

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consisting of D12S1657, D12S393, D12S1706, and D12S346 in the acellular DNA with the same DNA markers in a control DNA, determining from the comparison step if the acellular DNA has a loss of heterozygosity at one or more of the DNA markers; and predicting that the subject having a loss of heterozygosity at one or more of the DNA markers has a poor likelihood of responding to cancer therapy.

Claim 125 depends from claim 124 and draws the invention to wherein the cancer therapy is selected from the group consisting of chemotherapy, radiation therapy, gene therapy, immunotherapy, surgical procedure, and a combination of the cancer therapies.

Claim 126 depends from claim 124 and draws the invention to wherein the cancer therapy is biochemotherapy.

Claim 127 depends from claim 126 and draws the invention to wherein the cancer therapy is biochemotherapy and is a combination selected from the group consisting of dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2, and tamoxifen.

Claim 128 depends from claim 124 and draws the invention to wherein the acellular and control DNA are amplified.

Claim 129 depends from claim 124 and draws the invention to wherein the control DNA is obtained from non- neoplastic tissue from the subject.

Claim 130 depends from claim 124 and draws the invention to wherein the control DNA is obtained from a biological fluid or tissue from a normal subject.

Claim 131 depends from claim 124 and draws the invention to wherein the control DNA is obtained from peripheral blood lymphocytes from the subject.

Claim 132 depends from claim 124 and draws the invention to wherein the loss of heterozygosity comprises a 40% or more reduction of peak intensity for the acellular DNA marker as compared to the corresponding control DNA marker.

The amount of direction or guidance and the Presence and absence of working examples.

The specification teaches detection of D12S1657, D12S393, D12S1706, and D12S346 for diagnosis of melanoma, breast, or colon cancer. The specification sets forth no other uses for the claimed invention.

The specification teaches there is an unexpected LOH of markers for 12q22-23 in accellular samples (see page 3, lines 5-8). The specification further teaches that the 12q22-23 region encompasses the APAF-1 locus (see page 9, line 26) and there was a statistically significant allelic imbalance in metastatic tumors and primary melanoma ($p=0.02$)(see page 9, lines 28-29). Further APAF-1 loss was significantly correlated with a worse prognosis ($p<0.05$) (see page 10, 1st line). The specification further teaches melanoma patients that responded to chemotherapy had a significantly lower frequency of allelic imbalance at 12q22-23 ($P<0.029$) and better prognosis ($p<0.046$) (see page 10 line 12-13), then patients with an allelic imbalance. Further the specification teaches the use of 12q22-23 markers: D12S1657, D12S393, D12S1706, and D12S346.

The specification teaches LOH frequencies in primary melanomas tissue samples were 20%, 31%, 13% and 17% at D12S1657, D12S393, D12S1706, and D12S346, respectively (see table 1). The specification teaches LOH frequencies in metastatic melanomas were 23%, 35%, 17% and 21% at D12S1657, D12S393,

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D12S1706, and D12S346, respectively (see table 1). The specification asserts that there is a higher frequency of allelic imbalance in metastatic melanoma than primary melanoma ($P=0.02$), although there is no frequency differences between stage III melanoma and stage IV melanoma (see page 24, line 11 to page 15 line 1).

The specification further teaches there is no correlation between APAF-1 status and overall survival in primary melanoma tissue samples, but there is a statistically significant correlation between APAF-1 status and Stage III/IV melanoma ($p=0.05$) (see page 26, lines 10-15). Further survival of stage III metastatic melanoma and stage III metastatic melanoma with RLM was statistically correlated with APAF-1 status ($P=0.03$, $p=0.02$) but metastatic melanoma with ILM was not ($p=0.17$) (see page 26 line 25-page 26 line 3). It thus appears that LOH of D12S1657, D12S393, D12S1706, and D12S346 is correlated with survival of patients with stage III metastatic melanoma with RLM, but not survival with stage III metastatic melanoma with ILM. The specification is silent on LOH of D12S1657, D12S393, D12S1706, and D12S346 and stage IV melanoma.

Further the specification teaches the effect of allelic 12q22-23 in serum samples on melanoma patient outcomes. The specification teaches a significant relationship of allelic imbalance of D12S1657, D12S393, D12S1706, and D12S346 markers ($p=0.029$) before chemotherapy in the responder group (5 of 24), but not in the responder group after chemotherapy (9 of 24) (see page 36, line 11-15). It thus appears that chemotherapy resulted in 4 subjects having an LOH of the recited alleles in response to the biochemotherapy (see page 36, line 11-15). While 11 of 20 the non-responders had allelic imbalance before therapy, while only 7 of the 20 had allelic imbalance after

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therapy(see page 36, line 11-15). These teachings suggest that in 4 non-responders allelic imbalance can be restored in response to biochemotherapy.

Further patients with D12S1657, D12S393, D12S1706, and D12S346 LOH had a statistically significantly worse survival rate ($p=0.046$) (see page 36, line 17) than allelic imbalance negative subjects. The specification teaches response to dacarbazine (DTIC), cisplatin, vinblastin, interferon .alpha.-2b, IL-2, and tamoxifen was related to survival ($p<0.001$) (see page 36, line18).

The specification teaches only concurrent BC regimen of dacarbazine(DTIC), cisplatin, vinblastin, interferon .alpha.-2b, IL-2, and tamoxifen (see page 31, lines 13-17).

The specification does teach a statistically significant association of 12q22-23 LOH and melanoma, therapeutic response and outcome, but the specification teaches there is not a statistically significant relationship after chemotherapy, making the marker unpredictable for melanoma in those cases.

The specification does teach LOH in tumor samples of D12S1657, D12S393, D12S1706, and D12S346 are associated with melanoma and its progression and outcome. The specification teaches that the recited markers are associated with melanoma in primary tumors. The specification further teaches LOH of D12S1657, D12S393, D12S1706, and D12S346 is correlated with response in serum samples, before but not after chemotherapy.

Although the specification teaches LOH of D12S1657, D12S393, D12S1706, and D12S346 in de-proteinized blood is correlated with the resistance to

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biochemotherapy of melanoma, the specification provides no support that LOH of the recited alleles in urine, sputum, sperm, etc is correlated with melanoma, breast cancer, or colon cancer. The specification teaches, "it has been established that markedly increased concentrations of soluble DNA are present in plasma of individuals with cancer and some other diseases, indicating that cell free serum or plasma can be used for detecting cancer DNA with microsatellite abnormalities" (see page 8, lines 10-15). The specification appears to suggest that the acellular DNA is released into the serum or plasmid, however it does not teach or suggest the DNA from melanoma, breast or colon cancer would be present in sperm, feces, sputum, etc. It would thus be unpredictable to make such an association.

The state of prior art and the predictability or unpredictability of the art:

The prior art teaches that LOH D12S1657, D12S393, D12S1706, and D12S346 is common in metastatic melanoma (see abstract, Soengas, et al Nature, 2001, vol 409, 207-211). The prior art teaches D12S1657, D12S393, D12S1706, and D12S346 LOH is indicative of poor response to chemotherapy, (see page 209, column 1, lines 8-10). The prior art does not teach a correlation between D12S1657, D12S393, D12S1706, and D12S346 LOH and any cancer other than melanoma.

Gocke et al (US Patent 6156504, issued Dec 5, 2000) teaches methods of using of extracellular DNA found serum (2, 7) or plasma (claims 3,8,) for the detection of cancer (see title, abstract). Gocke teaches peripheral blood (claims 81, 82,); plasma or serum is easily accessible and amenable for DNA amplification (see column 2, lines 54-

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55). Gocke et al further teaches that many studies have used nucleic acid amplification to detect intracellular DNA extracted from circulating cells in blood (see column 2, line 56-60). Gocke teaches use of blood, plasma, or serum allows rapid and timely extraction and sensitive detection of extra cellular tumor associated or extracellular mutated oncogenic DNA (see column 3, lines 60-63).

Benner et al (Trends in Genetics (2001) volume 17, pages 414-418) teaches that, "Here, the 'homology-implies-equivalency' assumption is restricted to a subset of homologs that diverged in the most-recent common ancestor of the species sharing the homologs. This strategy is useful, of course. But it is likely to be far less general than is widely thought. Two species living in the same space, almost by axiom, cannot have identical strategies for survival. This, in turn, implies that two orthologous proteins might not contribute to fitness in exactly the same way in two species" (see page 414, 3rd column last full paragraph). Benner specifically describes that although the leptin gene homologs have been found in mice and humans, their affect is different (see page 414, 3rd column last paragraph-3rd column page 415). Benner specifically teaches that the leptin gene in mice plays a major role in obesity, but no such effect has been demonstrated in humans due perhaps to the different evolutionary forces. Benner thus teaches that the activity and function of genes in different species is unpredictable.

Fujiwara et al (Cancer Research (1999) volume 59, pages 1567-1571) teaches naked DNA released from tumor cells is released, enriched and remains stable in the blood of cancer patients and used for detecting cancer specific DNA markers (1567, 1st column, bottom). Fujiwara teaches genetic changes resulting progression of melanoma

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from stage II to stage IV are not well understood (1567, 2nd column, 2nd full paragraph).

Fujiwara teaches multiple LOH markers can be detected in the plasma of melanoma patients, but not healthy donors (1567, 2nd column, 2nd full paragraph). Fujiwara teaches, "The study also demonstrated that melanomas release tumor specific genetic markers in the blood that correlated to the patients respective melanoma legion" (1567, 2nd column, last paragraph). Fujiwara further teaches the frequency and number of microsatellite markers with LOH in plasma significantly increased in more advanced clinical stages of the (page 1570, 2nd column, 3rd paragraph). Fujiwara further teaches, "This study illustrates the clinical use or microsatellite analysis in detecting tumor DNA in plasma of melanoma patients. The analysis of LOH in plasma provides a logistically practical assay to monitor genetic changes during melanoma progression. The study demonstrates that at early clinical stages, release of DNA (LOH marker) is limited. Plasma LOH analysis may be more suitable to monitor stage II to stage IV progression before and during therapy as well as during post treatment 'follow-up. The markers may be also useful to detect subclinical disease recurrence in disease-free patients. Tumor progression is dynamic, and the genetic changes that concurrently occur are also ongoing. The most significant advantage of this approach in assessing plasma compared with direct analysis of tumor biopsies is the ability to monitor disease progression and genetic changes without assessing the tumor. This is particularly important during early phases of distant disease spread in which subclinical disease is undetectable by conventional imaging techniques. " Thus Fujiwara does not suggest that use LOH of acellular DNA markers is unpredictable, but suggests their use.

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Further Fujiwara teaches, " We and others have examined molecular markers such as melanoma- associated antigen mRNA markers in RT-PCR assays to detect melanoma cells in blood, lymph nodes, and various other organs. These molecular markers have been shown to be very useful in detecting metastatic melanoma cells and disease progression." Page (1570, 1st column). Fujiwara teaches LOH was a 50% reduction in the intensity of the allele relative to a normal matched lymphocyte (1568, 1st column). Fujiwara teaches the D3S1293 LOH is associated with disease progression.

O'Day et al (Journal of Clinical Oncology (1999) volume 17, pages 2752-2761)) teaches that different mono-therapies and combination therapies have different response rates.

The level of skill in the art:

The level of skill in the art is deemed to be high

Quantity of experimentation necessary:

In order to practice the invention as claimed one of skill in the art would first have to determine if it would be predictable to practice the invention relative to any control sample from any biological fluid or tissue from a "normal" subject. Thus would be unpredictable as the specification teaches that LOH was not found in the blood of a "normal subject." Further the specification and prior art has provided no evidence that the a control DNA from urine, hair, feces, etc have the DNA marker at the diploid level so as to allow one of skill in the art to determine a LOH such as to practice the invention as claimed. Further it would be unpredictable to practice the invention with any other species as the control DNA as the specification and prior art provide no evidence that

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any other species has genomic DNA that has the claimed markers. Further it would be unpredictable as Bennner teaches gene homologs of different species often have different functions due to different evolutionary pressure.

Further it would be unpredictable to detect responsiveness to any chemotherapy, radiation therapy, gene therapy, immunotherapy or surgical procedure as O'day et al teaches different chemotherapy agents have different response rates. Further the specification only provides data toward the efficacy of dacarbazine(DTIC), cisplatin, vinblastin, interferon .alpha.-2b, IL-2, and tamoxifen. Thus it would be unpredictable to use the claimed markers to determine efficacy of any cancer therapy without specific evidence. Further the only data about survival is following treatment with dacarbazine(DTIC), cisplatin, vinblastin, interferon .alpha.-2b, IL-2, and tamoxifen, thus it would be unpredictable to determine any survival as the specification and prior art lack any evidence the survival is increased in a subject without the treatment.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

6. Claims 118 and 127 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

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had possession of the claimed invention. The newly presented claims recited the limitation, "the cancer therapy is a biochemotherapy and is a combination selected from the group consisting of dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2, and tamoxifen." The specification teaches the biochemotherapy regimen is the combination of dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2, and tamoxifen. Thus by presentation of the claim as a combination of dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2, and tamoxifen the amendment has placed new limitations in the claims that are not supported by the claims and specification at the time of filing and thus are new matter.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 103-132 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "lower probability of survival" in claim 103 is a relative term which renders the claim indefinite. The term " lower probability of survival " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The claims do not set forth what the .lower probability s relative to. Claims 104-108 are rejected as they depend from claim 103.

The term "poor prognosis" in claim 109 is a relative term which renders the claim indefinite. The term "poor prognosis" is not defined by the claim, the specification does

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not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The claims should be amended to reflect what the poor prognosis is relative to. Claims 110-114 are rejected as they depend from claim 109.

The term "predicting the cancer therapy efficacy of the subject having a loss of heterozygosity of one or more of the DNA markers will likely be poor" in claim 115 is a relative term which renders the claim indefinite. The term " predicting the cancer therapy efficacy of the subject having a loss of heterozygosity of one or more of the DNA markers will likely be poor " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The claims should be amended to reflect what the poor efficacy is relative to. Claims 116-123 are rejected as they depend from claim 109.

The term "poor likelihood of responding" in claim 124 is a relative term which renders the claim indefinite. The term " poor likelihood of responding " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. . The claims should be amended to reflect what the poor likelihood of responding is relative to. Claims 125-132 are rejected as they depend from claim 109.

Claim Rejections - 35 USC § 103

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9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 103-117, 119-126, 128-132, are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) in view of Fujiwara et al (Cancer Research (1999) volume 59, pages 1567-1571).

Soengas et al teaches detection of loss of heterozygosity of 12q22-23 region in 24 patients using 6 12q22-23 microsatellite markers including D12S1657, D12S393, D12S1706, and D12S346 (see figure 1 and legend). Soengas further teaches genomic DNA for tumor and normal cells were amplified by PCR.

Soengas teaches loss of microsatellite markers (D12S1657, D12S393, D12S1706, and D12S346) in the 12q22-23 regions in patients are detected in metastatic melanoma (see abstract; page 207 2nd column, lines 12-14). Soengas further

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teaches genomic DNA for tumor and normal cells were amplified by PCR. Soengas teaches LOH of markers D12S1657, D12S393, D12S1706, and D12S346 is associated with loss of APAF1 expression (page 210, 2nd column).

Soengas teaches there is a high rate of APAF-1 LOH in metastatic melanoma (see page 207, column 2, lines 17-19), but not in primary melanoma (see page 208, 1st column, line 1). Soengas thus teaches LOH of APAF-1 in melanoma indicates a high probability of metastatic cancer.

Soengas teaches loss of APAF-1 is associated with disease progression (see page 208, lines 2-4).

Soengas teaches there is correlation of APAF-1 levels and response to Adriamycin in melanoma cells (see page 209, column 1, lines 8-10). Soengas teaches that APAF-1 levels are lower in melanomas with APAF-1 LOH. Soengas thus teaches APAF-1 LOH results in poor efficacy of treatment in melanoma.

Soengas does not teach the use of acellular DNA from plasma, serum, or blood as a sample.

However, Fujiwara teaches naked DNA released from tumor cells is released, enriched and remains stable in the blood of cancer patients and used for detecting cancer specific DNA markers (1567, 1st column, bottom). Fujiwara teaches genetic changes resulting progression of melanoma from stage II to stage IV are not well understood (1567, 2nd column, 2nd full paragraph). Fujiwara teaches multiple LOH markers can be detected in the plasma of melanoma patients, but not healthy donors (1567, 2nd column, 2nd full paragraph). Fujiwara teaches, "The study also demonstrated

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that melanomas release tumor specific genetic markers in the blood that correlated to the patients respective melanoma legion" (1567, 2nd column, last paragraph). Fujiwara further teaches the frequency and number of microsatellite markers with LOH in plasma significantly increased in more advanced clinical stages of the (page 1570, 2nd column, 3rd paragraph). Fujiwara further teaches, "This study illustrates the clinical use or microsatellite analysis in detecting tumor DNA in plasma of melanoma patients. The analysis of LOH in plasma provides a logistically practical assay to monitor genetic changes during melanoma progression. The study demonstrates that at early clinical stages, release of DNA (LOH marker) is limited. Plasma LOH analysis may be more suitable to monitor stage II to stage IV progression before and during therapy as well as during post treatment 'follow-up. The markers may be also useful to detect subclinical disease recurrence in disease-free patients. Tumor progression is dynamic, and the genetic changes that concurrently occur are also ongoing. The most significant advantage of this approach in assessing plasma compared with direct analysis of tumor biopsies is the ability to monitor disease progression and genetic changes without assessing the tumor. This is particularly important during early phases of distant disease spread in which subclinical disease is undetectable by conventional imaging techniques. " Thus Fujiwara does not suggest that use LOH of accellular DNA markers is unpredictable, but suggests their use. Further Fujiwara teaches, " We and others have examined molecular markers such as melanoma- associated antigen mRNA markers in RT-PCR assays to detect melanoma cells in blood, lymph nodes, and various other organs. These molecular markers have been shown to be very useful in

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detecting metastatic melanoma cells and disease progression.” Page (1570, 1st column). Fujiwara teaches LOH was a 50% reduction in the intensity of the allele relative to a normal matched lymphocyte (1568, 1st column). Fujiwara teaches the D3S1293 LOH is associated with disease progression.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Soengas method of detecting markers D12S1657, D12S393, D12S1706, and D12S346 by use of peripheral blood, plasma, or serum as taught by Fujiwara, for detection of markers associated with melanoma progression because Fujiwara teaches blood, plasma, or serum is easily accessible and amenable for DNA amplification and thus detection of nucleic acids. The ordinary artisan would further be motivated because, Fujiwara teaches, “The most significant advantage of this approach in assessing plasma compared with direct analysis of tumor biopsies is the ability to monitor disease progression and genetic changes without assessing the tumor. This is particularly important during early phases of distant disease spread in which subclinical disease is undetectable by conventional imaging techniques.” Thus as Fujiwara teaches methods of nucleic acid analysis by PCR amplification as taught by Soengas the artisan would have a reasonable expectation of success. The combination of Soengas and Fujiwara would have resulted in a method of detecting the presence or absence of D12S1657, D12S393, D12S1706, and D12S346 markers in acellular DNA from blood, serum, or plasma and from this detection allow prediction of probability of survival, prognosis, efficacy and response to therapy as Soengas teaches the loss is associated with a loss of response to

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chemotherapeutic agents and Fujiwara teaches increasing LOH results in poor prognosis and is associated with more advanced melanoma.

Response to Arguments

The arguments with respect to the Declaration by Dr. Hoon have been addressed above.

The response provides no specific arguments to the instant rejection other than asserting the teachings of Fujiwara do not specifically address the claimed markers. These arguments have been thoroughly reviewed but are not considered persuasive as Soengas is being relied upon for such teachings.

12. Claims 118 and 127 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al (Nature, 2001, volume 409, pages 207-211) in view of Fujiwara et al (Cancer Research (1999) volume 59, pages 1567-1571) as applied to claim 103-117, 119-126, 128-132, above, and further in view of Chapman et al (Journal of Clinical Oncology.(1999) volume 17, pages 2745-2751), Healy (oncogene (1998) volume 16, pages 2213-2218) and O'Day et al (Journal of Clinical Oncology (1999) volume 17, pages 2752-2761).

The claim 118 and 127 are drawn to biochemotherapy being selected from a group consisting of dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2, and tamoxifen.

The teachings of Fujiwara and Soengas are set forth above.

Soengas and Fujiwara do not teach that loss of heterozygosity of D12S1657, D12S393, D12S1706, and D12S346 is predictive of response to biochemotherapy or

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predicted efficacy of response to biochemotherapy from the group consisting of dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2 and tamoxifen.

However, Soengas teaches "Assessment of Apaf-1 status may therefore improve the therapeutic management of patients with malignant melanoma" (see page 210, 2nd column last line of text).

Chapman teaches, " patients with stage IV melanoma, based on American Joint Committee on Cancer (AJCC) criteria, have a universally poor prognosis with a median survival time of 3 to 11 months, depending on subgroup analyzed" (page 2745, 1st column). Chapman teaches, "Although initial response rates have often been encouraging in single-institution trials (typically 40% to 50%), subsequent phase II trials have not confirmed these response rates,9-14 and prospective phase III trials failed to demonstrate a superiority of many of these regimens over dacarbazine alone" (page 2745, 1st column). Chapman further teaches, "Patients with metastases confined to soft tissue sites (skin, lymph nodes, or lung) are more likely to respond to chemotherapy and, in many databases, have a better prognosis than patients with metastases to other sites. Of the 226 patients assessable for tumor response, 99 (44%) had metastasis confined to soft tissue sites. In this group of patients, the response rate to the Dartmouth regimen was higher than the response rate to dacarbazine (32% v 14%), with the difference reaching statistical significance. Despite a higher rate of tumor responses in patients with soft tissue metastases treated on the Dartmouth arm, there was no improvement in overall survival. This is not surprising given that, in both treatment arms, the response rates were relatively low and there were no complete

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responses. The European Organization for Research and Treatment of Cancer Melanoma Cooperative Group has reported a similar observation in which interleukin-2–based treatments doubled the response rate but had no apparent impact on survival.³¹ Other subsets of patients were analyzed (women and patients with visceral metastases), but no increase in response rate or survival was observed for the Dartmouth arm” (page 2750, 1st column). Thus Chapman teaches that subjects with stage IV melanoma have a poor response to treatment, poor survival time, and thus poor efficacy of response to treatment, although those with soft tissue metastasis were more likely to respond to treatment.

Healy teaches, “Some (but not all) studies on DNA ploidy in melanoma have suggested that individuals with tumours exhibiting aneuploidy have a poorer outcome” (page 2213, 2nd column, last paragraph). Healy further teaches, “metastatic melanoma is a late stage of disease, and nearly all patients with metastases will eventually die from their melanoma” (page 2213, 2nd column, last paragraph). Healy further teaches, “However, based on the FAL scores, the results suggest that the overall level of genomic instability (as well as losses of 6q and 10q) may determine the clinical behavior of the melanoma and the ultimate clinical survival. This association of higher FAL scores with a poorer clinical, outcome, independent of the depth of invasion, suggests that this variable might allow the identification both of individuals with thin melanomas who will eventually die from their tumour and of subjects with paradoxically thick melanomas in whom the melanoma will not metastasize.” (page 2215, 2nd column, last paragraph).

Further O'Day et al teaches "5-day modified concurrent biochemotherapy regimen of dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alpha-2b, and tamoxifen was repeated at 21-day intervals" (see abstract). O'Day teaches pretreatment evaluation (page 2753, 2nd column). O'Day further teaches, "the concurrent biochemotherapy regime of Legha et al was modified in an effort to reduce toxicity further while maintaining or improving efficacy. These modifications consisted of decrescendo IL-2 dosing, routine use of growth factor support with granulocyte colony-stimulating factor (G-CSF), and low-dose tamoxifen. The total IL-2 dose was unchanged, but this agent was administered in a decrescendo schedule, with a higher initial dose in the first 24 hours that decreased progressively on subsequent days. This change in IL-2 dosing is based on preclinical and clinical studies suggesting that decrescendo dosing improves efficacy and reduces cumulative IL-2 toxicity.^{29, 30} Routine post treatment G-CSF was implemented because of the high incidence of grade myelosuppression, fever/neutropenia, and infection in Legha's concurrent biochemotherapy trial. Tamoxifen was added to the regimen because at the time the study was designed, data suggested potential synergistic effects with chemotherapy" (page 2753^{1st} column, 2nd full paragraph).

Therefore, it would be prima facie obvious to one of skill in the art at the time the invention was made to predict long term survival (efficacy of response) of stage IV melanoma to dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alfa-2b, and tamoxifen in patients or the probability of responsiveness to dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alfa-2b, and tamoxifen in view of the

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teachings of Soengas and Fujiwara with a reasonable expectation of success.

Chapman and Healy teach that subjects with stage IV melanomas and metastasis had poor longer term prognosis and thus poor response to biochemotherapy. Chapman teaches only 5% to 20% of subjects with stage IV melanoma responded to biochemotherapy, while Healy teaches genomic instability plays a large role in clinical outcome. The teachings of Soengas suggest that loss of heterozygosity of D12S1657, D12S393, D12S1706, and D12S346 markers results decreased apoptosis, which in turn results in increased chemoresistance to chemotherapeutic agents in melanoma. Thus, it would have been obvious to one of skill in the art that subjects with stage IV melanoma and LOH of markers known to be associated with decreased apoptosis in melanoma in response to treatment a chemotherapeutic drug (adriamycin) would also be associated with decreased apoptosis and thus chemoresistance to other known chemotherapeutic agents (dacarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alfa-2b, and tamoxifen). It would have been obvious to one of skill in the art in view of the teachings of Soengas and O'Day to use D12S1657, D12S393, D12S1706, and D12S346 to predict responsiveness or efficacy of treatment as Soengas teaches "Assessment of Apaf-1 status may therefore improve the therapeutic management of patients with malignant melanoma" (see page 210, 2nd column last line of text). The artisan would be motivated because Soengas and Fujiwara suggest such a method as cited above. The artisan would have a reasonable expectation of success as the artisan would merely be using an assay to predict the response to a known biochemotherapy.

Response to Arguments

The response reiterates the arguments previously presented with respect to Soegnas and Fujiwara. These arguments have been previously addressed.

Summary

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN POHNERT whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Steven C Pohnert/
Primary Examiner, Art Unit 1634